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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/599,400	06/22/00	SAVITZKY	K 24286

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EXAMINER	
PRASAD,S	
ART UNIT	**PAPER NUMBER**
1646	18

DATE MAILED: 08/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/599,400	Savitzky et al.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3,4,6-8,12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,5,9-11,38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

Restriction/Election

1. Applicant's election with traverse of Group I (claims 1-2, 5, 9-11, and 38) directed to SEQ ID No. 1, in Paper No. 17 (6/25/01) is acknowledged. The traversal is on the ground(s) that claims directed to a product (Group I, claims 1-2, 5, 9-11, and 38), and a method of using the product (Group XXV, claims 16-21; and Group XXXIII, claims 22-24) should not be restricted. When product claims are deemed allowable, the method of using the product will be rejoined with the allowable claims.

Applicants argue that restriction of the sequences 1-8 in the generic claim, representing splicing variants of TNF receptor is improper, and they should not be restricted (page 4, 1st para of Paper No. 15, 3/12/01). Furthermore, the Applicants cite the 1192 OG 68 (November 19, 1996) and MPEP 803.04 with respect to "reasonable number" of sequences for examination purposes is quoted as 'normally 10'. However, the 'up to ten independent and distinct nucleotide sequences' for examination as a guideline for restriction purposes is true when such examination does not create an undue burden on the Office. However, this argument is not true in the instant case because the sequences 1-8 of the instant application constitute polynucleotides encoding structurally and functionally distinct alternate splicing variants. Therefore, Applicants' arguments to examine the sequences 1-8 in a single application is not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3-4, 6-8, 12-37 are withdrawn from consideration and currently, claims 1-2, 5, 9-11, and 38 are under consideration by the Examiner.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-2, 5, 9-11, and 38 are rejected under 35 USC § 101 because they are drawn to an invention with no apparent or disclosed utility.

The instant application has provided a description of TNF receptor splice variants and their possible biological activities. The breadth of its biological functions and possible uses have been disclosed in the specification are largely dependent upon the structural homology of the instant splice variants to TNF receptor (see entire text, and particularly pages 8-9, summary of the invention).

The instant invention lacks patentable utility because the phenomena of the ligand TNF or TNF–like ligands binding to their receptor and transduction of the signal for the claimed effectiveness and functionality of the instant TNF variants are hypothetical. It is clear from the instant specification that the alternately spliced variant of SEQ ID No. 1 exhibits 99% homology to naturally occurring TNF receptor. There is little doubt that, after further characterization, these variants will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicants' claim of utility of the instant TNF receptor variants is incomplete.

The instant situation is analogous to that which was addressed in Brenner v Manson, 148 USPQ 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which are known to possess anticancer activity was alleged to be a potential

antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-here is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and a "patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to polynucleotides that encode alternately spliced variants of the well known and well characterized human TNF receptor 1 gene (p60) between residues 1-217, with just a 2 amino acid deletion at the C-terminus, however, as of yet not shown to have distinct identity by way of demonstrated biological effects or functions. Until some actual and specific significance can be attributed to the polypeptides identified in the specification as SEQ ID NO. 1, the instant invention is incomplete. In the absence of knowledge of the biological significance of the polypeptides, there are no immediately obvious patentable uses for these TNF receptor splice variants. Since the instant invention does not disclose a "real world" use for proteins of SEQ ID NO. 1, the claimed invention is incomplete, and therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claims 1-2, 5, 9-11, and 38 are also rejected under 35 U.S.C.§112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112-First paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant written description sets forth a polynucleotide of SEQ ID No. 1 encoding a polypeptide of SEQ ID No. 9 representing a splice variant of TNF receptor, exhibiting 99% identity to TNF receptor (see attached sequence comparison), while differing by a C-terminal deletion of 2 amino acid residues. However, the written description is not commensurate with a claim reciting 'an isolated nucleic acid sequence of an alternative splicing variant that has 90% identity to SEQ ID No. 1' (sub-parts ii of claim 1) or 'fragments of SEQ ID No. 1 or a nucleotide sequence possessing at least 90% identity to SEQ NO. 1' (sub-part iii of claim 1).

Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the claimed invention. Therefore, the Applicant is not in possession of the invention as claimed, at the time of filing. This is insufficient to support the claims as provided by the Revised Written description Guidelines published in the Federal register, vol 66, No.4, pages 1099-1111, Friday January 2001.

Support for the variants is provided in the specification (pages 19-20, Example 1). However, no support is provided for the proposed amino acid changes to achieve 90% identity to

SEQ ID No.1, or fragments of at least 20 base pairs, and yet have any of the features/properties of TNF receptor. The general knowledge and level of skill in the art do not supplement the omitted description because the disclosure fails to describe what are the permitted and amino acid replacements while making changes to achieve alternate splice variants with 90% identity to SEQ ID No. 1, and fragments of SEQ ID No. 1. Therefore, it is not feasible for one of skill in the art to practice the invention as claimed. Therefore, it can be reasonably concluded that Applicant was not in possession of the claimed variants.

Claims 2, 5, 9-11, and 38 are rejected insofar as they depend on claim 1.

3b. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a splice variant of TNF receptor identified by an isolated nucleic acid of SEQ No. 1 encoding a polypeptide of SEQ ID No. 9, does not reasonably provide enablement for alternative splice variants of TNF receptor which have 90% identity with SEQ ID No. 1, or fragments of at least 20 base pairs containing a sequence not present, as a continuous stretch of nucleotides in the original sequence of SEQ ID No. 1, or a sequence that is 90% identical to SEQ ID No. 1 from which the alternately spliced variants have been derived. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1 is overly broad in the recitation of 'an isolated nucleic acid which is at least 90% identical to SEQ ID No. 1' (sub-parts ii), and 'fragments of at least 20 b.p., provided that said fragment contains a sequence which is not present " (sub-part iii) since no guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain any of the characteristics of a TNF receptor. In the specification, Applicants disclose that variants of the

polypeptide can be generated (Example 1, page 19) and expected performance parameters of the possible variants (Table 1, page 18). However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid sequence encoding a splice variant, at least 90% identical to that SEQ ID No. 1 that would encode a polypeptide with features of TNF receptor. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Given the breadth of claim 1 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the

instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 2, 5, 9-11, and 38 are rejected insofar as they depend on claim 1.

Claim Rejections - 35 USC § 112-Second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2, 5,9-11, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claim 1 (sub-part i) reciting 'the nucleic acid sequence depicted in any one of SEQ ID NO. 1 to SEQ ID NO. 8' is vague and indefinite because currently the claims are being examined with respect to SEQ ID No.1 only. This rejection can be obviated by reciting in sub-part (i) the nucleic acid consisting of SEQ ID NO. 1.

4b. Claim 5 is vague and indefinite because it is dependent on non elected claim 3 or 4. This rejection can be obviated by amending the claim to depend from one of the elected claims, either 1 or 2.

4c. Claims 9 and 10 are vague and indefinite in reciting 'an expression vector comprising any one of the nucleic acid sequences of Claim 1' because when claims 1 and 2 should be reciting only SEQ ID No. 1, it would be confusing to have expression vectors comprising any one of nucleic acid sequences of claim 1 or claim 2 respectively in claims 9 and 10.

4d. Claim 1 (sub-part iii) is vague and indefinite in reciting '...at least 20 b.p...'. Use of acronym b.p. for base pairs is confusing. Acronyms are subject to change and they may even be used in more than instance. This rejection can be obviated by reciting '....at least 20 base pairs...'.

Claims 11, 38 are rejected insofar as they depend on claims 1-2, 5, 9-10.

Conclusion

5. No claims are allowable.

Prior art of record:

Michael J et al. A soluble form of CD137 (ILA/4-1BB), a member of the TNF receptor family, is released by activated lymphocytes and is detectable in sera of patients with rheumatoid arthritis. 1998, Eur. J. Immunol. Vol.28, pages 290-295.

Weinshenker et al. Genetic Variants in the tumor necrosis factor receptor 1 gene in patients with MS. 1999, Neurology, vol.22, pages 15---1503.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
August 20th , 2001

Yvonne Eyler
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